When a Drug

Is In Short Supply

Infantile spasms, or West's syndrome, is a sometimes crippling and even life-threatening seizure disorder that affects about 3,000 babies a year in the United States. The only drug that helps prevent the spasms is Acthar gel, and the drug's only manufacturer is Rhone-Poulenc Rorer Pharmaceuticals Inc.

For several months in 1996, Rhone-Poulenc stopped making Acthar because of manufacturing difficulties. A crisis resulted, with insufficient supplies to treat patients with West's syndrome and other diseases.

While the company worked with the Food and Drug Administration to fix problems in its plant, the nonprofit National Organization for Rare Disorders helped dole out the very limited supplies for emergency cases of infantile spasms and other conditions. "During the shortage, even some people with severe pain from rheumatoid arthritis couldn't get the drug in favor of babies with life-threatening West's syndrome," says NORD president Abbey Meyers.

Severe drug shortages like this one are infrequent, but a minor supply problem creating a potential shortage usually arises about once or twice a month, says Mark Goldberger, FDA's coordinator for new drug review shortages.

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Medical Necessity

Potential drug shortages are a top agency priority, according to Mark Lynch, a branch chief in FDA's division of drug manufacturing and product quality. "Shortages call for rapid communication among the key people within FDA," he says. "Those

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involved have to drop what they're doing and react rapidly to the crisis."

But a reduction in the drug supply doesn't always warrant this emergency status. To be defined as a high-priority drug shortage, the drug must be found to be "medically necessary." The FDA division responsible for the drug leads the determination of medical necessity. The division considers several factors, including:

- the opinion of health professionals about the drug's usefulness,
- the seriousness of the medical condition, and
- the availability of acceptable brand-name or generic alternatives.

For example, a dangerous drug shortage occurred a few years ago when the supply of the anemia drug Desferal (deferoxamine mesylate) suddenly dropped. Desferal is the standard treatment for a fatal blood disease called Cooley's anemia. In 1995, an FDA inspection uncovered some manufacturing problems at the Swiss facility of the former Ciba-Geigy Corp., the only plant where Desferal was made, leading to a plant shutdown.

"We were fearful about the potential danger to patients based on the fact that there was no alternative source for Desferal," says Gina Cioffi, national executive director of the Cooley's Anemia Foundation. "Our patients must use this drug every day, or they're taking time off their life as iron builds up in their blood."

In a drug shortage situation like the one involving Desferal, FDA takes steps to find alternative sources of the drug or to control the distribution to make sure the most needy patients have access to it.

"These are acute problems that need to be addressed swiftly, with either a resolution or a short-term fix," Goldberger says. "If you've got a drug like Acthar that you need to prevent mental retardation or a drug like Desferal that you need to prevent iron overload, you can't take years. You either have to make it available quickly or figure out a substitute drug."

Increasing the Supply

The review division and office of compliance in FDA's Center for Drug Evaluation and Research work with manufacturers and third parties to find ways to keep a drug available despite various obstacles. "It's a problem-solving exercise," Lynch says. "Each situation is different; each drug is different; and the people are different each time."

The Acthar gel shortage was "different" because the drug is made from animal pituitary glands. "Because it is not synthetic, it is a difficult drug to manufacture," Goldberger says. "We worked with Rhone-Poulenc to bring the product to market while not placing an unrealistic burden on the company."

Sometimes FDA must take steps to avoid a drug shortage when the agency takes regulatory action, such as seizure or injunction, against a company. If shutting down a plant while the manufacturer corrects problems could lead to a shortage of a medically necessary drug, the agency may exempt that drug from the ban to keep it available.

To decide whether to make an exception for a certain drug, FDA must balance two risks: the risk from the noncompliance—for example, a manufacturing violation could result in a slightly less potent medication—and the risk of not having the product available at all.

For example, in spite of manufacturing problems, FDA allowed Ciba-Geigy's Desferal (as well as two other medically necessary drugs) into the United States from the firm's Swiss facility. FDA compliance officer Richard Friedman checked the quality of each lot of Desferal entering the country by analyzing extra data submitted by the company. "We worked closely with the firm to assure that products made it to pharmacies without delay and with no sacrifice in quality," Friedman says.

In other cases, a manufacturer may decide to stop making a drug simply because it is not a money-maker. In these cases, FDA or the National Organization for Rare Disorders may speak with other companies about making up the void. "To a big company, a market of $10 million or $20 million usually isn't enough," says

NORD president Meyers, "but to a small company, that market might be attractive." (See sidebar below.)

Other times, because of poor planning or an unforeseeable event such as a plant explosion or fire, a company may not have the usual amount of time required to get agency approval of a manufacturing change, such as a move to a new plant. If an interruption in manufacturing may lead to a dangerous drug shortage, FDA can expedite its inspection of the new plant or its review of required applications.

In cases where a company is experiencing a temporary delay in production, FDA may talk to other companies who have the facilities to make the product for the short term, or the agency may see if the manufacturer has some extra stock in its plant or warehouse that can help bridge the gap.

Managing the Demand

When a product is in dangerously short supply, the manufacturer or another party may set up an allocation program. That way, the drug is shipped directly to those who need it, rather than being shipped in large quantities to sit in a warehouse.

"Without a controlled allocation program," Goldberger says, "it's kind of like a gasoline shortage. Everyone rushes out and keeps their tanks full, and by keeping their tanks full, there's less gasoline to go around for those who really need it. If people just filled up when they needed to, you might not have a shortage."

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Coordinator for New Drug Review Shortages

To make sure anemic patients possessed only the amount of Desferal they really needed, Ciba-Geigy set up a distribution schedule to ensure that pharmacies only gave out a two-week supply at a time. "The company responded quickly by coming up with a distribution plan to make sure there was no gap in getting patients their drug," says Cioffi.

Shared Responsibility

Usually, dire shortages that require rationing can be avoided. Communication with the company and with specialized organizations such as NORD is the key, according to Goldberger.

The earlier FDA becomes aware of a possible shortage of a critical drug, the more effectively the agency can deal with it. "Part of the responsibility lies with the companies," Friedman says. "They should inform us as soon as possible if they anticipate a shortage of a medically necessary product."

FDA can sometimes help to avert a crisis or minimize the harm to patients if a shortage does occur. But, Goldberger says, "There are certain steps you have to go through to manufacture a product and get a product out on the market. FDA can speed up the process—find bridges—but we can't abolish it altogether, or we couldn't be sure of the drug's quality."

No Shortage of Incentives

The Orphan Drug Act, a 1983 addition to the Federal Food, Drug, and Cosmetic Act, offers financial incentives to the developer of a drug for a rare disease, including tax credits for clinical research and a seven-year period of exclusive marketing. FDA's Office of Orphan Products Development identifies orphan products and aids their development with guidance and grants.

A rare disease is one that affects fewer than 200,000 Americans or a population so small that U.S. sales would not cover the cost of developing the drug. There are 5,000 such diseases, which affect a total of 20 million Americans, according to Abbey Meyers, president of the National Organization for Rare Disorders.

"The act has been very successful in attracting companies," Meyers says. Since its passage in 1983, FDA has approved more than 140 drugs for rare conditions, compared with only 10 such approvals in the decade before 1983.